# The Physiology of Human Growth

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MICHAEL H.L. SNOW

# Embryonic growth and the experimental manipulation of fetal size

## Introduction

The weight of a newborn mammal, which in normal circumstances is characteristic of the species under consideration, is not simply a reflection of gestation length and/or nutrition but principally is determined genetically through growth rate. Analysis of fetal weight and conception age suggests that mammals can be segregated into three or four groups each having a different growth rate. Irrespective of whether the species displays fast, intermediate or slow growth the overall rate through late embryonic and fetal development is quite smooth, with no noticeable periods of fast or slow growth. There is a gradual decline in the rate from fast in early development to a slower rate as birth approaches (Snow, 1986 for review). Significant departures from the predicted growth curve, either above or below the norm, are regarded as pathological and have a correlation with abnormalities of various sorts (Neligan *et al.*, 1976; Spiers, 1982; Gould, 1986; Jones, Peters & Bagnall, 1986).

What then is known of the controls over embryonic growth?

## Maternal influences vs embryonic genotype

It is clear that maternal size is to some extent reflected in fetal size, small mothers tending to have small babies and vice versa. There is also a maternal effect associated with parity, and in polytocous animals an effect of litter size. Part of these phenomena will be a function of the genotype of the fetus and part the physiology of the mother – fetal crowding or undernutrition obviously serving to restrict fetal growth, whether the major controlling factors reside in fetal genotype or in maternal physiology. Analyses of the uterine effect on birthweight of hybrids or of embryos surgically transferred between large and small strains of various species have been recently reviewed (Snow, 1986). It seems clear that a large uterus will to some extent facilitate the growth of a small genotype embryo but a small uterus severely constrains the growth of a large genotype embryo. Most of these studies measured birth weight and therefore do not give any information about the shape of the fetal growth curve, which would show at what time the effect on fetal growth was operative. Aitken, Bowman & Gould (1977) analysed fetal weight at 16.5 days *post coitum* (dpc) in the mouse, which has a gestation of about 19 days. They found no

evidence for a uterine effect at that stage, either on small genotype or large genotype embryos when transferred to the intermediate sized surrogate mothers of the parental stocks. Since in the mouse a negative correlation between litter size and fetal weight has been found at 17.5 dpc and 18.5 dpc and at birth (Healy, McLaren & Michie, 1960; McCarthy, 1965; McLaren, 1965) it would appear that the constraining influence on fetal growth is a phenomenon of late pregnancy. A similar conclusion can be drawn from the growth curves of human twin fetuses which show a lowered birth weight in comparison to singletons. Twin fetuses, irrespective of zygosity, are of comparable size to singletons until the last 10–12 weeks of pregnancy during which their individual growth rate falls (McKeown & Record, 1952; Kloosterman, 1970).

Classically, fetuses were regarded as being in competition with one another for a limited supply of nutrients, this providing a simple explanation for the observed decline in weight with increased fetal numbers. This view was challenged by the data of Healy *et al.* (1960) and McLaren (1965) who observed that there were effects on mouse fetal weight associated with the number of implants per uterine horn (as opposed to total litter size), and the position within the norm. Moreover dead fetuses (presumably no longer competing for food) exerted the same effect as live ones. These authors proposed that the fetal weight data in the mouse could be explained by relation to blood supply, with those implants nearest the point of inflow of blood to the uterus being at a growth advantage over those further downstream. However in the rat, which has a similar uterine blood circulation, the distribution of fetal weights does not accord with this haemodynamic theory. Barr, Jensh & Brent (1970), Bruce & Norman (1975) and Barr & Brent (1970) have shown that an intact arterial blood supply is not necessary to establish the characteristic distribution of fetal weights in this animal. Direct measurement of blood flow to fetuses, whilst revealing variability, does not show a correlation with either litter size or fetal position (Buelke–Sam, Holson & Nelson, 1982). Thus fetal competition, limiting nutrition and blood flow seem inadequate explanations for the fetal weight distribution in rodents. It remains plausible that the late decline in fetal growth reflects physical constraint and that the effect of position within the uterine horn may be associated with slight spatial differences in the ease with which implantation is achieved, thus conferring a few hours' advantage to fetuses at certain sites.

There is no appropriate published data of litter size/fetal position/fetal weight relationships for stages prior to 17.5 dpc in the mouse but unpublished data gathered in my laboratory on some 40 normal 14.5 dpc litters show a slight positive correlation between litter size and fetal weight. This positive correlation is increased if litter size is experimentally reduced by unilateral ovariectomy or fallopian tube removal: fetal weight is increased in such conditions (Gregg, 1985). This observation is curious and unexpected; should the positive correlation stand up to further analysis questions are raised about possible feedback mechanisms linking embryo number with a growth

stimulating function in the pregnant female. In any case it seems unlikely that further data would establish a significant *negative* correlation between litter size and 14.5 dpc fetal weight, so it seems reasonable to conclude that embryonic and early fetal growth is not dictated by maternal environment, but is a reflection of embryonic genotype.

### Growth control in early embryos: sex differences

Experimental manipulation carried out on preimplantation embryos which either reduces embryo size (by blastomere removal) or increases it (by aggregation together of several embryos) does not result in smaller or larger fetuses. A change in cell proliferation rate shortly after implantation compensates by regulating size either up or down (see Snow, 1986 for references and discussion). Although the upward regulation needs a novel acceleration in cell proliferation in the embryo it is not possible to exclude an influence of growth factors from the pregnant female. Similarly the apparent regulation of embryo size to a postulated 'norm' during primitive streak stages (Snow, 1986) could also be controlled by maternally derived factors. However recent data have shown sex associated differences in embryonic growth and development rate which must be inherent in the embryo. Seller & Perkin–Cole (1987) have shown that in 8.25 dpc mouse embryos the least well developed embryos tend to be female rather than male, and lag behind by about 2 somites; according to the somite number/age curves of Tam (1981) this represents some 2–3h delay. A previous study demonstrated that XO monosomic embryos lag behind XX sibs (Burgoyne, Tam & Evans, 1983) and the unpublished data on XY embryos gathered in those studies show the male embryos to be further advanced than XX females, by about 1–2 somites at 9.5 dpc. My own unpublished data show the same degree of developmental advance in male embryos at 8.5 dpc. The sex difference seems to be generated during cleavage, since transfer of early cavitating blastocysts to foster mothers yields litters in which the sex ratio is skewed towards males, whilst the late cavitating group produces more females (Tsunoda, Tokunaga & Sugie, 1985).

### Genetic selection for size

In mice selected for large and small body size at 6 weeks of age a twofold difference in weight can be established (Falconer, 1955, 1973). Comparisons of embryonic development in these mice reveals no difference in cleavage rate prior to implantation (Bowman & McLaren, 1970) but it sems that growth rates begin to diverge shortly after that since a significant difference in embryonic sizes reported at around 8 dpc, at the onset of organogenesis (Gauld, 1980).

Analyses aimed at identifying the processes underlying the growth rate differences show that in the large strain mouse both cell number and cell size are increased. Cell number increase has the greater overall impact (Falconer, Gauld & Roberts, 1978) but there are organ-specific variations. In liver and kidney the relative contribution of

increased cell number and increased cell size seem about equal but in spleen and lung about 70% of the increase in size was found to be due to increased cell number. It was noted that males generally had larger organs than females, significantly so in lungs and kidney. Falconer *et al.* (1978) noticed in a comparison of mice at 3 weeks and 15 weeks that the cell size increment between these times was proportional to the respective amounts of growth made in the selected lines. Comparison of the selected lines at the same body weight but different ages indicated organs of similar cell number and cell size. Falconer therefore postulated that the selection process acted on differences in the relationship between chronological age and developmental age.

It is thought that the curious double peaked postnatal growth velocity curve found in primates, including man, may similarly reflect the slowing and expansion of the developmental timetable (Watts, 1986). Other mammals show a uniform gradual deceleration in postnatal growth. In the context of the size-selected mice it might be anticipated that the larger line would show certain developmental events occurring later in the growth curve. Data of precisely this sort is not available but Blakely (1979) found that the maximum elongation rate of fetal tibias occurred one day later in *small* strain animals. If this aspect of growth rate is related to the developmental timetable of hind-limb development then the relationship seems to be the wrong way round.

Blakely's data also show that large-genotype tibias have a significantly higher growth rate *in vitro* and furthermore that culture medium 'conditioned' by addition of 'large' embryo extract consistently (but statistically not significantly) supports better growth of tibias of all genotypes. The implication that some humoral growth factor may be involved needs to be tempered by the results of a detailed search which failed to find a growth controlling organ/centre which might have been the source of such a factor (Falconer, Gauld, Roberts & Williams, 1981; Snow, 1986 for discussion).

### Embryonic growth control: the whole vs the parts

Even a cursory glance over the tables of embryonic development for any species, mammalian or not, vertebrate or not, cannot fail to notice that development is normally a highly coordinated process with all parts of the embryo undergoing their morphogenesis in harmony with one another. A large volume of literature on induction and cellular and tissue interactions points to the fact that conversation between parts is essential to maintain normal development and may be closely restricted in time and space (Lehtonen & Saxen, 1986). It is equally clear that the relative proportions of organs within the animal change during the course of embryonic, fetal and postnatal development, eventually assuming the adult format. Thus parts of the embryo/fetus show their own individual growth profiles. Some of these data and the mechanisms which may be involved have been recently reviewed (Goss, 1986; Brasel & Gruen, 1986).

It has been found in the mouse that the growth of parts and its coordination can be profoundly disturbed in early embryonic (primitive-streak) stages by insult with cytotoxic agents (Snow & Tam, 1979; Snow, Tam & McLaren, 1981; Snow, 1983, 1987). Implementation of novel, changed growth profiles of parts for 3 to 5 days during organogenesis restores almost complete anatomical normality before birth and permits further development to adulthood in about 40% of the offspring. Detailed study of the embryonic development of these mice reveals some features of relevance to growth control and its relationship to morphogenesis (Tam, 1981; Tam & Snow, 1981; Gregg, 1985; Snow & Gregg, 1986).

First of all, in the general increase in cell proliferation rate that occurs throughout the embryo following reduction in cell number, ectodermal tissues seem able to raise their mitotic rate to a greater level than mesodermal tissues. Mesoderm however maintains an elevated rate for longer. This results initially in a large divergence from the normal ratio of ectodermal to mesodermal tissue, which is manifest as a neural tube adopting a wavy form along the axis of the embryo. The discrepancy in size is corrected as the growth rate in the neural tube slows while that in the mesoderm continues at an elevated level. These two cell lineages also behave differently in the morphogenetic timetable. The neural tube, after a short delay in the raising of headfolds, proceeds through development according to the normal chronological time scale whereas various parts of the mesodermal lineage (somites, limbs, vascular system, haemopoietic system) show developmental delay of different magnitudes (Snow, 1987).

Primordial germ cells suffer a population depletion in proportion to the rest of the embryo and the subsequent acceleration of cell proliferation they undergo is restricted both in duration and in the site within the embryo in which it occurs. Thus the mitotic rate is doubled only for the 24h period during which the germ cells are migrating across the mesentery from the hind gut to the dorsally situated genital ridge. This time limitation for restoration of germ cell numbers leads to gonads forming with a reduced germ cell population (Tam & Snow, 1981). As a result adult females who suffered cytotoxic insult as embryos have small ovaries with reduced numbers of oocytes and males present testes which may contain seminiferous tubules devoid of germ cells. Fertility is reduced in consequence.

The features of this restorative growth are consistent with the view that mesoderm morphogenesis requires that a critical mass of tissue is produced before differentiation can occur whereas no such constraint operates for ectodermal tissues. It cannot be claimed that tissue mass is a trigger for differentiation, since in untreated embryos structures are much larger than in treated embryos at the time when such processes commence. Thus it seems unlikely that growth/differentiation is controlled simply by titration of humoral factors against tissue mass; rather, individual cell lineages and organ systems have the ability to regulate their growth either in response to tissue-

specific growth factors or by autonomous active deployment of receptors for non-specific growth factors.

Examination of the skeletal phenotype of newborn mice following cytotoxic damage at primitive streak stage reveals a very high proportion of mice with extra vertebrae in the presacral spinal column (Gregg & Snow, 1983). Analysis of the course of development of these phenotypes (Gregg, 1985, and in preparation; Snow & Gregg, 1986) shows that at the time the skeletal pattern is changed the cells which will be involved in the generation of the extra vertebra(e) are located in the primitive streak or tail bud of the embryo and will not emerge as a segmented somite until some 12–15h later. Comparison with many other circumstances which generate extra vertebrae identifies elevated growth rate as the only clear similarity between them and leads us tentatively to suggest that this aspect of skeletal patterning may be a function of cell proliferation rates at crucial stages of development.

Overall, our experiments with cytotoxic agents and the resulting changed embryogenesis provide a dramatic example of how chronological age and developmental age can be altered and illustrate some of the morphological consequences of such a shift. It is clear that although anatomical changes are found they are not of a grossly abnormal nature. Whilst it must be concluded that the high postnatal mortality is a result of the damage to the early embryos, presumably indicative of more subtle errors in anatomy, physiology or biochemistry, the existence of long term survivors who appear quite normal is testimony to the remarkable ability for development to tolerate and then correct, by modulation of organ growth, profound disturbances to its normal pattern.

### Growth factors

Growth control in the embryo is clearly manifest, at both a general and local level, from stages prior to organogenesis. For these early stages there is little direct evidence for the production and functioning of either growth factors or their receptors. However, circumstantial evidence, for instance from studies with teratocarcinoma stem cells and from work on oncogenes with known growth regulating activity (see Adamson, 1987 for review), implicates several such factors.

Growth hormone does not normally cross the placenta in significant quantities and endogenous sources become active only in comparatively late fetal stages. Even in transgenic mice carrying additional rat or human growth factor genes the effects of production of extra growth hormone are seen only in postnatal mice, embryonic and fetal development apparently being normal (Palmiter *et al.*, 1982, 1983). Thus it can be concluded that growth hormone is not active in embryonic growth control.

Insulin likewise is only produced in fetal stages (Hill, 1976, and this volume) and it also does not cross the placenta so seems unlikely to be involved in embryonic growth control. However Sadler (1980) reports a growth promoting effect of insulin on 8 dpc mouse embryos cultured *in vitro* and Heath, Bell & Rees (1981)

demonstrate the appearance of insulin receptors during differentiation of embryonal carcinoma (EC) cells. These cells are commonly regarded as equivalent to the undifferentiated primitive ectoderm of primitive streak stage embryos, from which they have often been derived. Since insulin is teratogenic when administered via the pregnant female to embryonic stages as early as 8 dpc (Cole & Trasler, 1980) the possibility that it is indeed active in growth control in the embryo remains to be definitely resolved.

The somatomedins (insulin-like growth factors) also seem unlikely candidates for embryonic growth control since their function appears to be growth hormone dependent (see Clemmons, this volume). Nevertheless, the recent demonstration (Han, D'Ercole & Lund, 1987) that they are produced by the mesenchymal (connective tissue?) element of a wide range of human fetal organs must generate speculation that they may have a role in the control of embryonic development, particularly as mesenchymal connective tissue would be a good candidate for the growth controlling organ sought in vain by Falconer *et al.* (1981) in the chimaeric large ↔ small mice (see Snow, 1986 for discussion).

Epidermal growth factor (EGF) receptors are present in 10 dpc mouse embryos (Hortsch *et al.*, 1983) and on trophoblast tissue developed in blastocyst outgrowth, which are equivalent to about 7 or 8 dpc (Adamson & Meek, 1984). However the embryo/fetus does not appear to make EGF itself until around birth (Popliker *et al.*, 1987).

Transforming growth factor α (TGFα), which has homology with EGF and binds to EGF receptors, producing the same effects, has been found in 7 dpc mouse embryos (Twardzik, 1985), and could plausibly act via EGF receptors to modulate early embryonic growth. The other family of transforming factors, the TGFβ group, has known growth regulating functions, both inhibition and stimulation, in embryonic/fetal systems (see Massagué, 1987 for review). TGFβ is widely distributed in normal tissues and will stimulate expression of the c–sis oncogene in mouse embryo fibroblasts. The c–sis gene product is homologous to the B chain of platelet derived growth factor (PDGF) and is found to be expressed in the 4–5 week old human placenta (Goustin *et al.*, 1985). EC cells also make PDGF and it has been suggested that embryonic/fetal growth could be modulated locally by interaction between TGFβ and PDGF (Adamson, 1987).

Two other oncogenes, c–fos and c–myc, are of interest in the context of embryonic growth. The products of both genes are DNA binding proteins the c–fos protein controls passage of cells from G0 to G1 in the cell cycle and the c–myc protein regulates DNA synthesis. C–fos seems to be involved in cell differentiation and c–myc in cell proliferation (see Adamson, 1987 for review). All stages of mouse embryos that have been examined express c–myc; c–fos is expressed in 7 dpc mouse conceptuses but predominantly in the extraembryonic components. In mouse fibroblasts in which c–sis is induced by TGFβ the release of the PDGF-like factor

seems to stimulate activation of c–fos and then of c–myc. Both oncogenes are expressed in EC cells, c–fos at low levels in undifferentiated cells but increasing as differentiation proceeds; c–myc is maximally expressed during proliferation of the stem cells and declines with differention. c–myc and c–sis are co-expressed in the human placenta (Goustin *et al.*, 1985). Although the relationships between c–sis, c–fos and c–myc need clarification, a growing volume of literature seems to support the notion of a cascade involving all three in that order, possibly triggered initially by TGFβ (Adamson, 1987). Unfortunately, in the context of embryonic growth where prolonged cell proliferation precedes differentiation the expression of c–fos and c–myc seems to be in the reverse order to what would be expected.

Clearly many questions concerning the deployment of growth factors and oncogene products in early embryos are still to be answered but it remains most likely that the factors controlling growth will be found amongst these molecules.

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